REMARKS

Reconsideration of the above referenced application is respectfully requested. Upon entry of the foregoing amendment, Claims 88 and 90-95 are presently pending. Claims 72-87 have been withdrawn. Claims 1-71 and 89 have been cancelled without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter of the cancelled claims in one or more continuation or divisional application. No new matter has been introduced and entry of this amendment is respectfully requested.

Election/Restriction

Applicants confirm the provisional election of Group II (Claims 88-95), with traverse. Claims 72-87 have been withdrawn.

Rejection under 35 U.S.C. §112, first paragraph, enablement.

Claims 88-95 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement.

The Office Action maintains that Claims 88-95 are directed to methods of treating cancer of the bladder by treating the luminal surface of the bladder with a composition comprising an oncolytic virus and a transduction enhancing agent. The Office Action further states that while being enabling for treating a superficial tumor in the luminal surface of the bladder with a transduction enhancing agent according to formulas I or II in Claim 88 and subsequently contacting the bladder with an oncolytic virus, the specification does not reasonably provide enablement for treatment of cancer in the muscular layer of the bladder. The Office Action further states that the specification does not enable one of skill in the art to use the invention commensurate with the scope of the claims.

The first paragraph of 35 U.S.C. § 112 requires that the specification of a patent enable any person skilled in the art to which it pertains to make and use the claimed invention. Although the statute does not say so, enablement requires that the specification teach those in the art to make and use the invention without undue experimentation (e.g., In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir., 1991). An invention is enabled even though the disclosure

may require some routine experimentation to practice the invention. Hybritech Inc. V. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986).

In accordance with the accepted standards of enablement set forth above, an invention is enabled if one skilled in the art could make and use the claimed invention without undue experimentation.

Applicants submit that one of skill in the art relying on the disclosure in the specification would know how to treat cancer of the bladder by contacting the luminal surface of the bladder with a pretreatment composition comprising a transduction enhancing agent having a structure represented by the general formula (II) and an oncolytic adenovirus which exhibits preferential expression in the bladder epithelium, commensurate with the scope of Claim 88 and claims dependent thereon.

In view of the above amendments and remarks, withdrawal of the rejection under 35 U.S.C. § 112 is respectfully requested.

Rejection under 35 U.S.C. §103(a).

In the Office Action, the Examiner sets forth a number of grounds for rejection under 35 USC §103, each of which is discussed in detail as they apply to the current claims, below.

Claims 88-95 stand rejected under 35 U.S.C. § 103(a), as allegedly obvious over Zhang et al. (Cancer Res. 62:3743-3750, 2002) in view of Heidrun et al. (US Patent 5,789,244).

On page 6 of the Office Action, Zhang et al. is cited as allegedly teaching that adenovirus CG8840 was a urothelium-specific adenovirus variant that eliminates bladder tumors when administered at 3.33×10^9 pfu in combination with docetaxel.

Heidrun et al. is cited as allegedly teaching methods of treating bladder cancer by intravesical administration of adenoviral vectors and that adenoviral transduction of bladder tissue could be improved by disruption of the epithelial glycoaminoglycal layer by pretreatment of the bladder with a delivery enhancing agent such as sodium lauryl sulfate.

On page 6, the Office Action concludes that it would have been obvious to one of skill in the art at the time of the invention to modify the method of Zhang et al. by applying adenovirus to the luminal surface of the bladder as taught by Heidrun et al. The Office Action states that it would have been obvious to use the method in vivo, and one would have been motivated to use luminal delivery in order to improve access to tumors in the bladder epithelium.

Applicants respectfully disagree.

As stated in MPEP §2142, the examiner bears the initial burden of factually supporting a prima facie conclusion of obviousness. The examiner must show that the claimed invention was obvious to a person of ordinary skill in the art at the time the application was filed. To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

To establish a *prima facie* case of obviousness the prior art reference (or references when combined) must teach or suggest all of the claim limitations. In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991) and MPEP § 2142. Moreover, when applying 35 U.S.C. § 103, the following tenets of patent law must be adhered to: (A) The claimed invention must be considered as a whole; (B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and (D) Reasonable expectation of success is the standard with which obviousness is determined. Hodosh v. Block Drug Co., Inc., 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

Zhang et al. do not teach administration to the luminal surface of the bladder or the use of a transduction enhancing agent.

Heidrun et al. do not teach administration of a replication competent virus, nor do they teach or suggest compounds having a structure such as compound II of Claim 88. Heidrun et al. is directed to a "a gene delivery system" which refers to any means of delivery of a therapeutic gene to a particular epithelial tissue or organ. Heidrun et al. describe delivery-enhancing agents, such as lauryl sulfate and provide a list of representative agents, which does not include a structure represented by the general formula II, as presently claimed.

It follows that the combination of Zhang et al. and Heidrun et al. does not teach or suggest a method of treating cancer of the bladder comprising contacting the luminal surface of the bladder with a pretreatment composition comprising a transduction enhancing agent having a structure represented by the general formula II, wherein x is a positive integer; and subsequently

contacting the luminal surface of the bladder with a composition comprising an oncolytic virus. Hence, the combined references do not teach or suggest all of the claim limitations.

Therefore, one of skill in the art relying on the combination of Zhang et al. and Heidrun et al. would not have a reasonable expectation of success in practicing the present invention. Therefore, a *prima facie* case of obviousness has not been established and the rejection should be withdrawn.

Claims 88-95 stand rejected under 35 U.S.C. § 103(a), as allegedly obvious over Watanabe et al. (Int .J. Cancer 92:712-171, 2001) in view of Heidrun et al. (US Patent 5,789,244) and Mullen et al. (Oncologist 7:106-119, 2002).

Watanabe et al. is cited as allegedly teaching methods of treating bladder cancer with replication deficient adenovirus carrying a suicide gene (ras) in a mouse model of bladder cancer, that the virus was instilled intravesically and inhibited the growth of superficial tumors. The Office Action states that Watanabe et al. did not teach an oncolytic virus or use of a transduction enhancing agent.

Heidrun et al. is described above and is relied upon as teaching that adenoviral transduction of bladder tissue could be improved by disruption of the epithelial glycoaminoglycal layer by pretreatment of the bladder with a delivery enhancing agent such as sodium lauryl sulfate.

Mullen et al. is cited as allegedly teaching that oncolytic viruses expressing therapeutic transgenes offered a distinct advantage over analogous replication defective gene therapy vectors because the virus amplifies itself through several rounds of replication allowing an increase in gene expression leading to an amplified anti tumor effect.

On page 8 and 9, the Office Action concludes that it would have been obvious to one of skill in the art at the time of the invention to modify the method of Watanabe et al. by treating mouse bladders with sodium lauryl sulfate and to substitute replication competent adenoviruses for replication defective ones.

Applicants respectfully disagree.

Watanabe et al. did not teach an oncolytic virus or use of a transduction enhancing agent.

As set forth above, Heidrun et al. do not teach administration of a replication competent virus, nor do they teach or suggest compounds having a structure such as compound II of Claim 88. Heidrun et al. describe delivery-enhancing agents, such as lauryl sulfate and provide a list of representative agents, which does not include a structure represented by the general formula II, as presently claimed.

Mullen et al. is cited as allegedly teaching the replication properties of oncolytic viruses.

The combination of Watanabe et al., Heidrun et al. and Mullen et al. does not teach or suggest a method of treating cancer of the bladder comprising contacting the luminal surface of the bladder with a pretreatment composition comprising a transduction enhancing agent having a structure represented by the general formula II and subsequently contacting the luminal surface of the bladder with a composition comprising an oncolytic virus. Hence, the combined references do not teach or suggest all of the claim limitations.

Therefore, one of skill in the art relying on the combination of Watanabe et al., Heidrun et al. and Mullen et al. would not have a reasonable expectation of success in practicing the present invention. Therefore, a *prima facie* case of obviousness has not been established and the rejection should be withdrawn.

Claims 88-95 stand rejected under 35 U.S.C. § 103(a), as allegedly obvious over Zhang et al. (Cancer Res. 62:3743-3750, 2002) in view of Heidrun et al. (US Patent 5,789,244) and Gaffar et al. (US Patent 5,368,844).

On page 10 of the Office Action, Zhang et al. is cited as allegedly teaching that adenovirus CG8840 was a urothelium-specific adenovirus variant that eliminates bladder tumors when administered at 3.33×10^9 pfu in combination with docetaxel. Page 10 of the Office Action further states that Zhang et al. do not teach administration to the luminal surface of the bladder or the use of a transduction enhancing agent that was an alkyl sulfate salt.

On page 10 of the Office Action, Heidrun et al. is cited as allegedly teaching methods of treating bladder cancer by intravesical administration of adenoviral vectors and that adenoviral transduction of bladder tissue could be improved by disruption of the epithelial glycoaminoglycal layer by pretreatment of the bladder with a delivery enhancing agent such as sodium lauryl sulfate.

Gaffar is cited as allegedly teaching that sodium lauryl sulfate and sodium dodecyl benzene sulfonate are anionic surfactants with similar performance characteristics.

On page 10 and 11, the Office Action concludes that it would have been obvious to one of skill in the art at the time of the invention to modify the method of Zhang et al. by applying the adenovirus to the luminal surface of the bladder, as taught by Heidrun, in order to treat bladder cancer. The Office Action further states that it would have been obvious to modify the method of Zhang et al. by treating mouse bladders with sodium lauryl sulfate or sodium dodecyl benzene sulfonate in order to improve access to tumors in the bladder epithelium.

Applicants respectfully disagree.

Zhang et al. and Heidrun et al. are described above.

Gaffar et al. is directed to an antiplaque, antigingivitis and anticaries oral compositions. One of skill in the art would appreciate that use of sodium lauryl sulfate or sodium dodecyl benzene sulfonate as an anionic surfactant for use in delivering an oral composition, such as an antibacterial agent does not teach or suggest the relative utility of such compounds in intravesical administration of oncolytic adenoviral vectors to bladder.

One of skill in the art would not be motivated to combine a reference such as Gaffar et al. which is directed to improving the properties of an antiplaque, antigingivitis and anticaries oral composition with references such as Zhang et al. (directed to a urothelium-specific adenovirus variant that eliminates bladder tumors when administered at 3.33×10^9 pfu in combination with docetaxel) and Heidrun et al. (directed to adenoviral transduction of bladder tissue).

Furthermore, one of skill in the art relying on the combination of Zhang et al., Heidrun et al. and Gaffar et al. would not have a reasonable expectation of success in practicing the present invention. The combination of Zhang et al., Heidrun et al. and Gaffar et al. does not teach or suggest a method of treating cancer of the bladder comprising contacting the luminal surface of the bladder with a pretreatment composition comprising a transduction enhancing agent having a structure represented by the general formula II and subsequently contacting the luminal surface of the bladder with a composition comprising an oncolytic virus. Hence, the combined references do not teach or suggest all of the claim limitations.

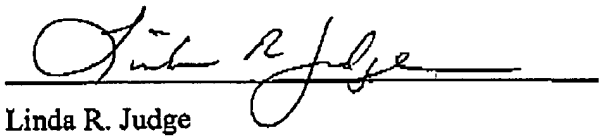
Therefore, a *prima facie* case of obviousness has not been established and the rejection should be withdrawn.

CONCLUSION

In light of the above, Applicants submit that this application is now in condition for allowance and therefore request favorable consideration. If any issues remain which the Examiner feels may be best resolved through a personal or telephonic interview, the Examiner is respectfully requested to contact Applicants' counsel, Linda R. Judge at (415) 836-2586.

Respectfully submitted,

DLA PIPER RUDNICK GRAY CARY US LLP



Linda R. Judge
Registration No. 42,702

1200 Nineteenth Street, N.W.
Washington, D.C. 20036-2412
Telephone No. (202) 861-3900
Facsimile No. (202) 223-2085